Evidence of a Healthy Estrogen User Survivor Effect

Susan R. Sturgeon,[1] Catherine Schairer,[1] Louise A. Brinton,[1] Thomas Pearson,[2,3] and Robert N. Hoover[1]

We examined the relation between menopausal estrogen use and all-cause and cause-specific mortality in a cohort of over 49,000 women followed between 1979 and 1989 in the Breast Cancer Detection Demonstration Project (BCDDP) Follow-Up Study. We found a lower all-cause mortality rate among women who took estrogens [rate ratio (RR) = 0.7; 95% confidence interval (CI) = 0.7–0.8], particularly current users (RR = 0.3; 95% CI = 0.2–0.4), than among women who never took them. Additional analyses, however, revealed that women who had recently stopped taking estrogens had a higher all-cause mortality rate than women who had never taken them (RR = 1.4; 95% CI = 1.2–1.7). Women who had recently stopped taking estrogens also had higher mortality rates from circulatory disease (RR = 1.3; 95% CI = 1.0–1.8) and cancer (RR = 1.6; 95% CI = 1.2–2.2) than women who never took them. The most likely explanation for these results is that women stop taking estrogens when they develop symptoms of serious illness. As a consequence of this "healthy estrogen user survivor effect," nonexperimental studies are susceptible to overestimating the benefits of menopausal estrogen use, particularly current use, on mortality. (Epidemiology 1995;6:227–231)

Keywords: menopausal estrogens, mortality, selection bias, cohort study.

Menopausal estrogen use has been related to reductions in mortality from virtually all causes, including cardiovascular disease, breast cancer, injuries, and diseases of the digestive and respiratory systems.[1–5] On the basis of these findings, it has been proposed that menopausal estrogens have a wide range of beneficial physiologic and biochemical effects, which, in turn, reduce mortality.[6] An alternative explanation for the observed nonspecific reduction in mortality associated with estrogen use is that healthier women selectively receive menopausal estrogens.[7,8]

To determine whether selection bias may account for at least some of the purported beneficial effects of menopausal estrogens on all-cause mortality, we examined data from a large cohort study in which exposure to estrogens was updated throughout the follow-up period. We specifically examined the relation of mortality to years since stopping estrogens, reasoning that an elevated mortality rate in the first few years after stopping estrogens would indicate that women are taken off this medication when they develop symptoms of serious illness. Such a pattern would also imply that healthier women preferentially receive estrogen therapy.

Methods

Between 1973 and 1975, the Breast Cancer Detection Demonstration Project (BCDDP) recruited over 280,000 women in 29 centers throughout the United States to participate, free of charge, in a 5-year program of annual breast examinations, including mammography. A subset of these women was selected for inclusion into a follow-up study, including: (1) 25,114 women who during screening had a breast biopsy, aspiration, or other breast procedure without ever receiving a diagnosis of breast cancer; (2) 9,628 women who received during screening a recommendation for a surgical consultation but did not ultimately undergo a procedure; and (3) 25,165 women who did not have a breast procedure or a recommendation for further surgical evaluation during screening.

A baseline questionnaire on menstrual and reproductive factors, oral contraceptive use, other female hormone use, family history of breast cancer, and history of benign breast biopsies before entry into the BCDDP was administered between 1979 and 1981 by trained telephone interviewers. Up to six annual follow-up telephone interviews updated this information. A second phase of follow-up involved the administration of one mail questionnaire between 1987 and 1989. Data on race, education, income, weight, and height were available from forms completed during the screening program.

The 49,017 women in the present study had completed a baseline interview and were menopausal and

From the [1]Environmental Epidemiology Branch, National Cancer Institute, Bethesda, MD; [2]Department of Epidemiology, School of Public Health, Columbia University, New York, NY; and [3]M. I. Bassett Research Institute, Cooperstown, NY.

Address correspondence to: Susan R. Sturgeon, Environmental Epidemiology Branch, National Cancer Institute, Executive Plaza North, 6130 Executive Boulevard, Room 443, Bethesda, MD 20892.

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free of breast cancer at the date of entry into the final analytic cohort. The date of entry was the date of the baseline questionnaire or the date of menopause, whichever was later. For women with a hysterectomy and at least one ovary retained, the date of menopause was defined as the date associated with the median age at natural menopause in the cohort (52.75 years) or the date of hysterectomy, whichever came later. The average age at entry into the cohort was 57.4 years; 84% of the total person-years were accumulated by women younger than age 70 years. A total of 89% of the subjects were white.

At the baseline questionnaire, women were asked whether they had ever used female hormones (excluding oral contraceptives and creams) and, if so, their age at first use and years of use. At each subsequent questionnaire, women were asked whether they had used female hormones since their last questionnaire and, if so, the duration of use. Female hormones that were taken more than 5 years before menopause were assumed not to be menopausal estrogens and therefore were not evaluated in this analysis.

Menopausal estrogen use was assessed in a time-dependent manner up until 1 year before date of death for deceased individuals or an equivalent time for alive individuals. For women who survived more than 1 year after their last questionnaire, we assumed that no additional estrogen use occurred between their last questionnaire and exit dates if they were ex-users or nonusers at their last questionnaire. For those women who survived more than 1 year after their last questionnaire and were current users at their last questionnaire, we classified their estrogen exposure between their last questionnaire and exit dates as unknown. It is likely, however, that many of these women were still using estrogens at their exit date.

Vital status was determined throughout the telephone follow-up period and during extensive tracing efforts related to the mail questionnaire. At the end of the follow-up period, defined as June 30, 1989, 95% of subjects were known to be alive, 4% were deceased, and 1% had unknown vital status. A copy of the death certificate was obtained on 91% of the reported deaths, and the underlying cause of death was coded by the study nosologist according to the rules of the ninth revision of the *International Classification of Diseases*.[9]

Accumulation of person-years began with the date of entry and continued until the end of follow-up, date of death, or date last known alive, whichever came earlier. Age-adjusted rate ratios (RR) and 95% confidence intervals (CI) for all causes and specific causes of deaths were obtained using Poisson regression.[10] Because of the high prevalence of hysterectomy and oophorectomy among estrogen users in this cohort, we excluded deaths from cancers of the female genital tract from all analyses. Adjustment for race, education, income, type of menopause, age at menopause, oral contraceptive use, and body mass index (kg per m^2) did not materially change the risk estimates presented in the text. In analyses focused on breast cancer mortality, additional adjustment for age at first livebirth, number of first-degree relatives with breast cancer, and number of benign breast biopsies did not the alter the findings.

Results

Menopausal Estrogen Use and All-Cause Mortality

In all age and race groups, the all-cause mortality rate was lower among women who had ever taken menopausal estrogens than among women who had never taken them (Table 1). This lower mortality among users resulted from reductions in mortality from most causes of death examined, including all cancers except lung cancer, endocrine, nutritional, and metabolic disorders, ischemic heart disease, other heart diseases, diseases of the respiratory and digestive systems, and injuries other than suicides (Table 2). Only mortality rates of infectious disease, lung cancer, cerebrovascular disease, and suicide were not substantially lower among estrogen users than nonusers.

Years since Last Menopausal Estrogen Use and Mortality

Further analyses that evaluated associations with years since last estrogen use focused on the following mortality outcomes: all causes, circulatory disease (total, ischemic heart disease, cerebrovascular disease, and other heart disease), cancer (total, colon, lung, breast, and leukemia/lymphoma), and all other specified causes.

Women who were currently taking estrogens had a lower all-cause mortality rate than women who had never taken them (RR = 0.3; 95% CI = 0.2–0.4) (Table 3). By contrast, women who had not taken estrogens for the past 2–3 years had an elevated mortality rate (RR = 1.4; 95% CI = 1.2–1.7). Women who had stopped taking estrogens in the more distant past had mortality rates that were similar to those of nonusers.

TABLE 1. Menopausal Estrogen Use and All-Cause Mortality* by Age and Race Category

Age (Years)	Whites		Other	
	Never-Users	Ever-Users	Never-Users	Ever-Users
<60				
No. of deaths	148	122	28	11
Person-years	69,649	66,791	10,059	7,455
Rate/100,000	212.5	182.7	278.4	147.6
60–74				
No. of deaths	388	422	70	48
Person-years	51,664	73,988	6,594	7,439
Rate/100,000	751.0	570.4	1061.6	645.2
≥75				
No. of deaths	329	191	54	13
Person-years	10,761	8,774	1,134	677
Rate/100,000	3057.3	2,176.9	4076.2	1,920.2

* Excludes cancers of the ovary, uterus, and other female genital organs.

TABLE 2. Menopausal Estrogen Use and Cause-Specific Mortality

Cause of Death (ICD)	Number of deaths		Age-Adjusted RR	95% CI
	Never-Users*	Ever-Users†		
All causes‡	1,017	807	0.7	0.7–0.8
Infectious (001–139)	9	9	1.0	0.4–2.5
Cancer (140–208)‡	346	301	0.8	0.7–0.9
Colon (153)	46	43	0.8	0.6–1.3
Pancreas (157)	36	28	0.7	0.4–1.2
Lung (162)	65	81	1.1	0.8–1.5
Breast (174)	53	43	0.7	0.5–1.0
Urinary (188, 189)	14	7	0.5	0.2–1.2
Lymphoma, leukemia§	48	42	0.8	0.5–1.2
Other cancers‡	84	57	0.6	0.4–0.8
Endocrine, nutritional, and metabolic (240–279)	25	14	0.5	0.3–1.0
Circulatory disease (390–459)	374	276	0.7	0.6–0.8
Ischemic heart disease (410–414)	199	142	0.7	0.6–0.9
Cerebrovascular disease (430–438)	60	56	1.0	0.7–1.4
Other heart disease‖	115	78	0.7	0.5–0.9
Respiratory (460–519)	55	45	0.8	0.5–1.2
Digestive (520–579)	27	25	0.8	0.5–1.4
Injuries (800–999)	31	20	0.6	0.3–1.1
Suicides (950–959)	5	7	1.6	0.5–5.1
Other injuries	26	13	0.5	0.2–0.9
Other specified causes	58	44	0.7	0.5–1.1
Unknown causes	92	73	0.8	0.6–1.1

* Person-years = 149,865 (referent group).
† Person-years = 165,127.
‡ Excludes cancers of the ovary, uterus, and other female genital organs.
§ Neoplasms of the lymphatic and hematopoietic tissue (200–208).
‖ Includes acute and chronic rheumatic fever (390–398), hypertensive disease (401–405), diseases of the pulmonary circulation (415–417), and other forms of heart disease such as endocarditis, pericarditis, and unspecified cardiovascular disease (420–429).

TABLE 3. Years since Stopping Menopausal Estrogens and All-Cause Mortality

Cause	Nonusers	Current Use*	Years since Former Use			Unknown
			2–3.9	4–5.9	≥6	
All-causes						
Age-adjusted RR	1.0	0.3	1.4	0.9	0.9	0.5
95% CI	(Referent)	(0.2–0.4)	(1.2–1.7)	(0.7–1.2)	(0.8–1.0)	(0.4–0.6)
No. of deaths	1,017	75	132	61	483	56
Person-years	149,865	54,483	18,951	11,810	66,767	13,114

* Includes women who last took estrogens in the past 1–1.9 years.

Women with incomplete information on their use of menopausal estrogens had an all-cause mortality rate that was intermediate between current and former users.

We evaluated the association between years since last use and cancer mortality (Table 4). Current estrogen users had markedly lower mortality rates of the specific cancers examined (that is, lung, breast, colon, and leukemia/lymphoma) than women who never took estrogens, whereas women who had stopped taking estrogens within the past 2–5 years tended to have higher rates of these cancers. Women who stopped taking estrogens in the more distant past had mortality rates of these cancers that were similar to, or for breast cancer, slightly lower than those of nonusers.

We present the relation between years since last use and circulatory disease mortality in Table 5. The pattern of RRs for ischemic heart disease mortality was inconsistent across the interval since stopping. Mortality was substantially reduced among current users, rose to 0.9 among those who had not taken estrogens for 2–3 years, and dropped again to 0.4 among those who had not taken them for 4–5 years. Women who had not taken estrogens for 6 or more years had a mortality rate similar to nonusers. Among women who had not taken estrogens for 6 or more years, results were similar with finer stratification on years since stopping estrogens.

Cerebrovascular disease and other heart disease mortality rates were lower among current estrogen users, but higher among those who stopped taking estrogens within the past 2–5 years, than among women who never took estrogens. Women who had not taken estrogens for 6 or more years had cerebrovascular disease and other heart disease mortality rates that were slightly lower than women who never took estrogens.

The mortality rate of other specified causes, such as injuries and diseases of the respiratory and digestive systems, was lower among current estrogen users (RR = 0.3; 95% CI = 0.2–0.5) but higher among women who stopped within the past 2–3 years (RR = 1.2; 95% CI = 0.8–1.9) than among women who never took them. Women who had not taken estrogens for 4 or more years had mortality rates that were similar to or lower than those of women who never took them (data not shown).

Years of Use and Mortality

Associations between mortality and duration of menopausal estrogen use were examined among women who stopped taking estrogens 6 or more years ago (Table 6). There were too few deaths to examine the effects of duration of use within the other strata of years since last use. There was a suggestion that mortality from ischemic

TABLE 4. Years since Stopping Menopausal Estrogens and Cancer Mortality

Cause	Nonusers	Current Use*	Years since Former Use 2–3.9	4–5.9	≥6	Unknown
All cancers†						
Age-adjusted RR	1.0	0.3	1.6	1.0	0.8	0.6
95% CI	(Referent)	(0.2–0.5)	(1.2–2.2)	(0.7–1.5)	(0.7–1.0)	(0.4–0.9)
No. of deaths	346	35	60	25	159	22
Breast						
Age-adjusted RR	1.0	0.1	1.4	1.5	0.7	1.1
95% CI	(Referent)	(0.1–0.5)	(0.6–2.9)	(0.7–3.5)	(0.4–1.2)	(0.2–2.5)
No. of deaths	53	2	8	6	21	6
Lung						
Age-adjusted RR	1.0	0.4	2.6	1.6	1.2	0.7
95% CI	(Referent)	(0.2–0.9)	(1.5–4.3)	(0.8–2.6)	(0.7–1.7)	(0.3–1.8)
No. of deaths	65	9	19	8	40	5
Colon						
Age-adjusted RR	1.0	0.4	1.8	1.2	1.0	0.2
95% CI	(Referent)	(0.2–1.0)	(0.9–3.7)	(0.6–2.7)	(0.5–1.6)	(0.1–1.5)
No. of deaths	46	6	9	4	23	1
Lymphoma/leukemia						
Age-adjusted RR	1.0	0.2	2.4	0.6	0.9	0.2
95% CI	(Referent)	(0.1–0.7)	(1.2–4.6)	(0.2–2.6)	(0.6–1.5)	(0.1–1.3)
No. of deaths	48	3	11	2	25	1

* Includes women who last took estrogens in the past 1–1.9 years.
† Excludes cancers of the ovary, uterus, and other female genital organs.

TABLE 5. Years since Stopping Menopausal Estrogens and Circulatory Disease Mortality

Cause	Nonusers	Current Use*	Years since Former Use 2–3.9	4–5.9	≥6	Unknown
Circulatory disease						
Age-adjusted RR	1.0	0.3	1.3	0.9	0.9	0.4
95% CI	(Referent)	(0.2–0.4)	(1.0–1.8)	(0.6–1.4)	(0.7–1.1)	(0.2–0.6)
No. of deaths	374	23	41	19	176	17
Ischemic heart disease						
Age-adjusted RR	1.0	0.3	0.9	0.4	1.0	0.4
95% CI	(Referent)	(0.2–0.5)	(0.5–1.5)	(0.2–1.1)	(0.7–1.2)	(0.2–0.7)
No. of deaths	199	13	14	5	101	9
Cerebrovascular disease						
Age-adjusted RR	1.0	0.4	3.3	1.5	0.9	0.3
95% CI	(Referent)	(0.2–1.0)	(1.9–5.8)	(0.6–3.8)	(0.6–1.5)	(0.1–1.9)
No. of deaths	60	5	16	5	28	2
Other						
Age-adjusted RR	1.0	0.2	1.2	1.4	0.7	0.4
95% CI	(Referent)	(0.1–0.5)	(0.6–2.1)	(0.7–2.7)	(0.5–1.0)	(0.2–1.0)
No. of deaths	115	5	11	9	47	6

* Includes women who last took estrogens in the past 1–1.9 years.

heart disease and leukemia/lymphoma decreased with increasing years of use. We saw no other pattern of decreasing risk with increasing years of use.

Discussion

Consistent with other investigators,[1–5] we found that women who took menopausal estrogens, particularly recent users, had a lower all-cause mortality rate than women who never took them. We also found, however, that women who recently stopped taking estrogens had a higher all-cause mortality rate than women who never took them. These results indicate that menopausal estrogen use is discontinued in women who develop symptoms of serious illness, with healthier women remaining on estrogen therapy. A healthy estrogen user survivor effect is likely to explain some of the decrease in all-cause mortality observed in this study among current users. Assuming that healthier women are also more likely to have ever used estrogens, the reduction in all-cause mortality among women who had taken any estrogens observed in this study could also be attributable, at least in part, to selection bias. In fact, in one of the few previous studies of all-cause mortality to address this potential bias,[4] the rate ratio for any estrogen use rose from 0.7 to 0.9, and the rate ratio for current estrogen use rose from 0.3 to 0.7, after excluding women with preexisting cancer and cardiovascular disease. In an updated analysis of data from the same cohort, the all-cause mortality rate ratio for any estrogen use was 0.9 in women free from diagnosed cancer and heart disease at baseline.[11] If it had been possible to exclude women with other preexisting conditions from these analyses, further attenuations in the reported effects might have been observed.

By contrast, several studies of mortality from cardiovascular disease suggest that differences in the prevalence of preexisting medical conditions between estrogen users and nonusers do not entirely account for the reduction in cardiovascular mortality among estrogen users. For example, Bush and colleagues[5] found that the relative risk associated with estrogen use only changed from 0.3 to 0.4 by excluding women with prevalent heart disease. Stampfer and colleagues[4] found a relative risk of 0.7 for any estrogen use, even after excluding women with prevalent cardiovascular disease. Henderson and colleagues[3] found a relative risk of 0.8 for any estrogen use among women who reported no prior history of angina or myocardial infarction. Excluding women with overt cardiovascular disease, however, may not be sufficient to compensate for the healthy estrogen user effect. For example, women who take estrogens, particularly current users, are more likely to engage in preventive behaviors, such as receiving more blood pressure checks, cholesterol testing, and cancer screening tests than women who do not take estrogens.[12] Petitti and col-

TABLE 6. Years of Menopausal Estrogen Use and Mortality among Women Who Stopped Taking Estrogens 6 or More Years Ago

Cause of Death	<5 Years of Use		≥5 Years of Use	
	Number of Deaths	Age-Adjusted RR*	Number of Deaths	Age-Adjusted RR*
All-causes†	306	0.9	177	0.9
All cancers†	100	0.8	59	0.9
Breast	11	0.6	10	1.0
Lung	24	1.1	16	1.3
Colon	15	1.0	8	1.1
Lymphoma/leukemia	18	1.1	7	0.7
Circulatory disease	117	0.9	59	0.8
Ischemic heart disease	71	1.0	30	0.8
Cerebrovascular disease	16	0.8	12	1.1
Other	30	0.7	17	0.7

* Referent group is nonusers.
† Excludes cancers of the ovary, uterus, and other female genital organs.

leagues[1] have proposed that this state of "healthiness" may be difficult to quantify and adjust for statistically.

Consistent with the results of Petitti *et al*,[1] we observed a lower mortality for injuries other than suicides among estrogen users. The recognized benefits of estrogens on osteoporosis and related hip fractures seem unlikely to account for our findings, owing to the relatively young age of the participants in the BCDDP cohort. Petitti and colleagues[1] have suggested that unidentified selection biases are likely to be responsible for the lower mortality from injuries associated with estrogen use.

An elevated suicide mortality rate among hormone users has been reported in one other study.[13] A possible explanation is that physicians are more likely to prescribe estrogens to women with clinical symptoms of depression than to those who do not have these symptoms. Because drugs with lipid-lowering effects have been linked with an elevated rate of suicides among men enrolled in clinical trials,[14] this finding deserves further attention.

We excluded women with preexisting breast cancers at entry into the cohort, and therefore, the lower mortality from breast cancer observed among users is not due to a lower proportion of women with preexisting breast cancer among users. In a separate analysis of data from this study,[15] breast cancer incidence was found to be similar among estrogen users and nonusers. Taken together, these findings imply that women who take estrogens before their diagnosis of breast cancer have a more favorable survival. Several other studies have reported similar results.[3,16] In view of evidence that estrogen use may be associated with smaller tumors,[15,17] a possible explanation for this observation is that menopausal estrogen use is associated with less aggressive tumors. Alternatively, these results may reflect unmeasured selection factors associated with estrogen use that lead to improved survival from breast cancer.

This study has several potential limitations. First, we were unable to adjust for some potential confounding factors, including cigarette smoking, alcohol consumption, and physical activity. Differences in these risk factors, however, are unlikely to account for the observed excess mortality among recent past estrogen users compared with nonusers. Another potential limitation is that our study cohort is highly selected, owing to their voluntary participation in a 5-year breast cancer screening project. The standardized mortality ratio (SMR), based on 1985 U.S. white female all-cause mortality rates, was substantially less than 1 (SMR = 0.42). It is unlikely, however, that the selection forces associated with participation in BCDDP were differential by estrogen use.

In summary, our data confirm earlier suspicions that menopausal estrogens are selectively prescribed to healthier women. The degree to which the healthy estrogen user effect may account for lower mortality rates among women who take estrogens will be difficult to resolve with nonexperimental studies.

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